

## **REMARKS**

The present Amendment is in response to the Examiner's Office Action mailed September 30, 2003. Claims 1-6 and 9-26 are amended. Claims 1-26 are now pending.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

### **I. Objection to the Specification**

The Examiner objects to abstract of the disclosure because it is not specifically directed to the subject matter of the instant claims. In response, Applicants submit herewith a new abstract to replace the original one.

The Examiner also objects to the disclosure for various informalities. In response, Applicants made the following amendments to the Specification:

- 1) the Brief Description of the Figures on page 4 amended to include description of FIG. 1A and FIG. 1B separately, support for which appears in the specification at page 18, lines 14-18;
- 2) the specification containing blank spaces correlated to attorney docket number amended to replace the attorney docket number with the corresponding U.S. patent application serial number now known to Applicants; and
- 3) the disclosure containing an embedded hyperlink amended to replace the website with browser-executable code with the one without.

### **II. Rejection under 35 U.S.C. §112, Second Paragraph**

Claims 1-21 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. In response, Applicants amend claims 1-3 to clarify the relations between the terms, "the four-way complex", "the tracer molecule" and "the detection molecule".

Applicants also amend claims 21 and 26 to replace the term “cy dyes” with “cyanine dyes”. As shown by Applicants’ numerous search results on the Internet, e.g., <http://cmgm.stanford.edu/pbrown/mguide/hplc.html>, one of ordinary skill in the art often use “cy dyes” and “cyanine dyes” interchangeably to refer to a class of fluorescent dyes.

In view of the above amendments and remarks, Applicants submit that claims 1-21 are sufficiently definite to one of ordinary skill in the art under 35 U.S.C. §112, second paragraph. Withdrawal of the rejection is therefore respectfully requested.

### **III. Rejection under 35 U.S.C. §102(e)**

Claims 1-26 are rejected under 35 U.S.C. §102(e) as being anticipated by Yang, et al. (2001) (U.S. 2002/0042061, filed 3/12/2001).

Independent claims 1 and 2 as amended each specifies a method for detecting a difference in the sequence of two nucleic acid molecules. As specified in claim 1 or 2, the two nucleic acid molecules are subject to conditions that allow them to form a four-way complex which undergoes branch migration. As illustrated in FIG. 1A, if the sequences of two nucleic acid molecules match each other, the four-way complex resolves into duplexes. As illustrated in FIG. 1B, if the sequences of two nucleic acid molecules mismatch each other, the branch migration is halted and the four-way complex is stabilized. This stabilized four-way complex competes with a tracer molecule (e.g., another four-way complex) for binding to a detection molecule (e.g., a protein such as RuvA that specifically binds to a four-way complex).

Further, claim 1 as amended specifies that detection of the difference between the two nucleic acid molecules can be achieved by comparing the binding of the tracer molecule to the detection molecule before and after exposure to the four-way complex. If the binding is reduced, it indicates that the four-way complex formed by the two nucleic acid molecules competes with the tracer molecule for binding to the detection molecule, which in turn indicates that there is a difference between the two nucleic acid molecules. *See* the specification, page 3, lines 31-35, and page 4, lines 1-3.

Alternatively, claim 2 as amended specifies that detection of the difference between the two nucleic acid molecules can be achieved by comparing the binding of the tracer molecule to

the detection molecule in the presence of the four-way complex, with that in a test sample in the absence of the four-way complex.

Nowhere in Yang et al. (2001) could be found a teaching or suggestion of a method employing a tracer molecule to detect a difference between two nucleic acid molecules by exploiting the competition between the four-way complex and the tracer molecule for the binding to a detection molecule. Thus, this reference fails to anticipate the claimed invention under 35 U.S.C. §102(e). Withdrawal of the rejection is therefore respectfully requested.

Moreover, under 35 U.S.C. §103(c) and pursuant to MPEP 715.01(b) which provides:

Where, however, a rejection is applied under 35 U.S.C. 102(f)/103 or 35 U.S.C. 102(g)/103, or, in an application filed on or after **November 29, 1999**, under 35 U.S.C. 102(e)/103 using the reference, a showing that the invention was commonly owned, or subject to an obligation of assignment to the same person, at the time the later invention was made would preclude such a rejection or be sufficient to overcome such a rejection (emphasis added).

Applicants submit here with a copy of the assignment recorded in Yang et al. (2001) to show that the claimed invention of the present application was commonly owned by Freshgene, Inc. at the time when the claimed invention was made.

In view of this showing of common ownership of the claimed invention and Yang et al. (2001), the cited reference is also not a prior art under 35 U.S.C. §103(c).

### **III. Rejection under 35 U.S.C. 102(b)**

Claims 1-11 and 17-21 are rejected under 35 U.S. C. 102(b) as being anticipated by Lishanski et al. (US Patent No: 6, 013,439).

As discussed in detail above, the claimed method employs a tracer molecule to detect a difference between two nucleic acid molecules by exploiting the competition between the four-way complex and the tracer molecule for the binding to a detection molecule.

In contrast, Lishanski et al. merely teaches formation of a Holliday complex and detection of the formed Holliday complex by detecting the changes in the **complex itself**. Specifically, Lishanski et al. teaches using two labels L1 and L2 on the complex to facilitate the

detection of the formation of Holliday complex. *See* Abstract and Figure 1. Lishanski et al. also teaches a “one-label” approach that requires “only one label, L1 or L2, which comprises an sbp member or a reporter molecule. A receptor for the sbp member and a receptor that can bind to complex C by virtue of a feature other than L1 or L2 can both bind to complex C and provides a means for detection”. Column 21, lines 26-30. Besides being vague and confusing, this teaching does not show one of ordinary skill in the art how the complex C may be labeled with one label and how the labeling would facilitate the detection, let alone teaching or suggesting the claimed invention of detecting the formation of a four-way complex via detection of the **competition between the four-way complex and a tracer molecule** for binding to a detection molecule.

In view of the distinct differences between the claimed invention and the teaching of Lishanski et al., the cited reference fails to anticipate the claimed invention under 35 U.S.C. §102(b). Withdrawal of the rejection is therefore respectfully requested.

### **III. Rejection under 35 U.S.C. 103(a)**

Claims 1-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lishanski et al. (US Patent 6,013,439) in view of Mezard et al. (IDS ref: Nuc. Acids Res. (1999) Vol. 27, No. 5, pp. 1275-1282).

As discussed in detail above, Lishanski et al. fails to teach the claimed invention of detecting the formation of a four-way complex via detection of the competition between the four-way complex and a tracer molecule for binding to a detection molecule. The secondary reference, Mezard et al., fails to supply the elements missing in Lishanski et al. to establish a prima facie case of obviousness. As acknowledged by the Examiner, Mezard et al. merely teaches Ruv proteins which specifically bind to Holliday junctions to form complexes, wherein the complex formed is a stable 4-way complex comprising 4 oligonucleotides. Page 1275.

In view of the distinct differences between the claimed invention and the deficient teaching or suggestion of Lishanski et al. and Mezard et al., a prima facie case of obviousness has not been established under 35 U.S.C. §103(a). Withdrawal of the rejection is therefore respectfully requested.

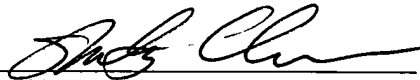
**CONCLUSION**

In light of the remarks and arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

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